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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/967,301	09/28/2001	Simon Lawrence John Stubbs	PA-0111	5224

22840 7590 03/31/2004

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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/31/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/967,301	STUBBS ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 13-25* is/are pending in the application.

4a) Of the above claim(s) *1-10 and 19-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *11,13-18 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response to the Office Action mailed October 24, 2003 on January 16, 2004 is acknowledged.

2. Claim 12 has been canceled. Claims 11, 13-18 and 25 have been amended. Claims 1-11 and 13-25 are pending. Claims 11, 13-18 and 25 are under examination.

3. The following rejections are or remain applicable:

Specification

4. The specification is objected to because of the following informalities:

The specification is objected to because on page 28, lines 18-19, it is disclosed that " F64L-S175G-E222G-GFP, and other cells or organelles with same or another fluor, fusions..." and it appears that there is a typo. The specification is also objected to because trademarks are disclosed and they are not capitalized. The use of the trademark such as TRIS®, ViewPlate and LEADsecker, etc., has been noted in this application (see for example, pages 35-36). It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 11, 13-18 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modified GFP comprising the amino acid sequences set forth in SEQ ID NOS: 2, 3 and 4 wherein the mutations are at positions 64, 65, 222 and 175, does not reasonably provide enablement for a modified GFP and any functional analogue. The specification is also not enabled for functional analogue of the sequences set forth above. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Factors considered in determining whether undue experimentation is required, are summarized in *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Circ. 1988). They include but are not limited to: quantity of experimentation, the amount of direction or guidance presented, the presence or absence of working example, the nature of the invention, the state of the prior art, the relative skill of those in the art, predictability or unpredictability of the art and breath of the claims. The factors will be discussed below.

The claims are directed to a nucleic acid molecule comprising a nucleotide sequence encoding a fluorescent protein which is derived from GFP or any functional

analogue, said protein is modified compared to the wild-type GFP protein. The specification fails to describe or provide any identifying characteristics or properties of the analogue or provides data to demonstrate that function is retained, even for the sequences recited in the claims (SEQ ID NOS: 2, 3 and 4). The specification does not describe/provide a structure or any characteristics of the claimed analogue, and is not enabled for any analogue. The term "analogue" does not have an art recognized definition, therefore, one of skill in the art would have to perform undue experimentation to determine what analogues of GFP and determine if said analogues retained the claimed biological function. Additionally, the claims are directed to a fluorescent protein derived from GFP that is modified in comparison to the wildtype. However, the claims do not establish if the GFP is from *A. victorea*, or *Renilla*, for example, thus, it unclear what GFP wildtype to make the comparison to. Due to the large quantity of experimentation necessary to generate the infinite number of analogues of GFP recited in the claims and possibly screen same for activity and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The specification sets forth that the claimed protein is contained in SEQ ID NOS: 2, 3 and 4, however, the claims broadly read on any analogues of the above proteins. The specification does not provide support for the broad scope of the claims, which encompass any analogues of the GFP derived from any species. Therefore, absent direction/guidance, one of skill in the art would not have been able to practice the claimed invention commensurate in scope with the claims.

The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in a certain activity, which is very complex, and well outside the realm of

routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure. Furthermore, while recombinant and mutagenesis techniques are known, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. For example, Heim et al. (PNAS, vol. 91, pages 12501-04, 1994) disclose that a mutated DNA was sequenced and found to contain five amino acid substitutions, only one of which was found to be critical, Tyr66His, in the center of the chromophore. Heim et al. also disclose further site directed mutagenesis and noted that there was tolerance of the substitutions made, however, some mutants were weakly fluorescent (page 12504). Therefore, while it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. Thus, the claimed nucleic acid encodes a protein that might not be functional or completely different from the wild type as the claims recite the open language comprising which indicates that mutations other than the recited four are included.

Additionally, the claims are directed to a modified form of a GFP protein, exhibiting a different excitation spectrum from a wild-type GFP, however, no maximum wavelengths of said peaks are defined. Therefore, absent direction/guidance regarding the structure of the analogue that can tolerate the modifications that will produce an excitation spectrum that differs from the wildtype, one of skill in the art would not have been able to practice the claimed invention commensurate in scope with the claims.

In view of the foregoing, one of skill in the art would require guidance, beyond that provided in the instant specification, in order to make a modified GFP and GFP analogues comprising the mutation recited in claim 1 in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 11, 13-18 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is indefinite as to a fluorescent protein "derived from GFP as there are many types of GFP and there is no indication in the claims as to which one the protein is derived. Additionally, the claim is indefinite because it is directed to a fluorescent product "derived" from a modified form of a wild type GFP, however, the metes and bounds of the term "derived" are not defined neither in the specification nor the art, rendering the claim unclear as there is no limitation on the number of changes in the wild-type structure that can occur. The term "functional analogue" is indefinite because the specification does not provide a definition that is limiting and there is no art-accepted definition. Claim 11 is also indefinite for the recitation of "said modified GFP has a different excitation spectrum compared to the wildtype", because it is unclear what "wild-type" to compare to, is it *A. Renilla* or *A. victorea*? In addition, as the wild type is undefined a different "excitation spectrum compared to the wild-type" is relative. The claim is further indefinite as it is unclear whether the difference in the excitation

spectrum is an improvement, how does the modified GFP spectrum differ from the wildtype? The dependent claims hereto are also included in this rejection. See also claim 14.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 11 is rejected under 35 U.S.C 102(b) as being anticipated by Bastiaens et al. (WO 00/08054, 17 February 2000) based on any functional analogue of GFP having the mutations set forth in the claims.

Bastiaens et al. teach polynucleotides encoding fluorescent proteins obtained from (GFP) having mutations at positions F64, S65 and S175. As claim provides no indicia about the structure of the analogue, the sequence set forth in SEQ ID NO: 2 of the reference is considered to be one such analogue (see abstract of the reference). Thus, the limitations of the claims are met by this reference.

8. Applicant's response filed January 16, 2004 has been considered. Note that the rejections of record have been withdrawn, however, upon due reconsideration new grounds of rejections have been instituted for the reasons set forth above.

Conclusion

9. No claims are presently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S.F. Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS

Patent Examiner

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER